Clinical Practice Guideline

Sickle Cell Disease

Quick Reference Guide for Clinicians

Number 6

Sickle Cell Disease: Comprehensive Screening and Management in Newborns and Infants

- Screening
- Laboratory Methods
- Diagnosis
- Medical Management
- Education and Counseling

U.S. Department of Health and Human Services
Public Health Service
Agency for Health Care Policy and Research

Attention clinicians:

The *Clinical Practice Guideline* on which this *Quick Reference Guide for Clinicians* is based was developed by an interdisciplinary, private-sector panel comprising health care professionals and consumer representatives. Panel members were:

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For a description of the guideline development process and information about the sponsoring agency (Agency for Health Care Policy and Research), see the *Clinical Practice Guideline for Sickle Cell Disease: Screening, Diagnosis, Management, and Counseling in Newborns and Infants* (AHCPR Publication No. 93–0562). To receive additional copies of the *Clinical Practice Guideline,* which includes this *Quick Reference Guide* (AHCPR Publication No. 93-0563), and a *Parent's Guide* (AHCPR Publication No. 93–0564), call toll free 800-358-9295 (from outside the continental United States only, call 301-495-3453) or write the AHCPR Publications Clearinghouse, P.O. Box 8547, Silver Spring, MD 20907.

AHCPR invites comments and suggestions from users for consideration in developing and updating future guidelines. Please send written comments to Director, Office of the Forum for Quality and Effectiveness in Health Care, AHCPR, Executive Office Center, Suite 401, 2101 East Jefferson Street, Rockville, MD 20852.

Note: This *Quick Reference Guide for Clinicians* contains excerpts from the *Clinical Practice Guideline,* but users should not rely on these excerpts alone. Clinicians should refer to the complete *Clinical Practice Guideline* for more detailed analysis and discussion of the available research, critical evaluation of the assumptions and knowledge of the field, health care decision making, and references.

Sickle Cell Disease: Comprehensive Screening and Management in Newborns and Infants

Purpose and Scope

Sickle cell disease comprises a group of genetic disorders characterized by the inheritance of sickle hemoglobin (Hb S) from both parents or Hb S from one parent and a gene for an abnormal hemoglobin or beta-thalassemia from the other parent. The presence of Hb S can cause red blood cells to change from their usual biconcave disc shape to a crescent or sickle shape during deoxygenation. Upon reoxygenation, the red cell initially resumes a normal configuration, but after repeated cycles of "sickling and unsickling," the erythrocyte is damaged permanently and hemolyzes. This hemolysis is responsible for the anemia that is a hallmark of sickle cell disease. The following table includes the most common types of sickle cell disease.

Acute and chronic tissue injury can occur when blood flow through the vessels is obstructed by the abnormally shaped red cells. Complications include painful episodes involving soft tissues and bones, acute chest syndrome, priapism, cerebral vascular accidents, and both splenic and renal dysfunction. Common causes of mortality among children with sickle cell disease include bacterial infections, splenic sequestration crisis, and acute chest syndrome.

Sickle cell disease affects more than 50,000 Americans, primarily those of African heritage, but also those of Mediterranean, Caribbean, South and Central American, Arabian, or East Indian ancestry. It is estimated that 8 percent of the African American population carries the sickle cell trait, and approximately 1 African-American child in every 375 is affected by sickle cell disease. Thus, it is among the most prevalent of genetic diseases in the United States.

Types of Sickle Cell Disease

Sickle cell anemia	S-O Arab
Hemoglobin SC disease	S-Lepore
Sickle beta-thalassemia	S-E disease
S-D Punjab	

This *Quick Reference Guide* contains excerpts from the *Clinical Practice Guideline on Sickle Cell Disease: Screening, Diagnosis, Management, and Counseling in Newborns and Infants.* Clinicians should not rely on this summary alone but should refer to the *Clinical Practice Guideline* for a more complete discussion of issues and recommendations.

The algorithm, found on pages 8 and 9 of this *Quick Reference Guide*, shows the sequence of events related to sickle cell screening, diagnosis, medical management, and counseling in newborns and infants. This *Quick Reference Guide* provides information about the events listed in the algorithm.

Guiding Principles

- All infants should be screened for sickle cell disease, regardless of race or ethnic background.
- Sickle cell screening must be done by accurate laboratory methods.
- Physicians must establish a definitive diagnosis in a timely fashion for infants with a positive screening test.
- Affected infants and parents must have access to comprehensive health care services, including education and decision-making counseling.
- Neonatal sickle cell screening programs also provide an opportunity to identify other members of the family with sickle cell trait and other abnormal hemoglobins. When these individuals are found, clinicians should offer them education and genetic counseling.

Screening

Neonatal screening programs for sickle cell disease should be comprehensive. Such programs require the integration of several components, including administration, laboratory, medical management, and education/counseling.

Administration

The administrative component should oversee the entire program, monitoring the efficacy of the screening initiative, the quality and accuracy of laboratory testing, the diligence of medical followup, and the activities of the education and counseling program.

The administrative group should include public health officials; geneticists; representatives from the laboratory; staff from the education and counseling program; physicians knowledgeable about sickle cell disorders, thalassemia, and other hemoglobinopathies; and when possible, representatives of community-based sickle cell organizations.

Population To Be Screened

Universal screening is the only way to ensure that all infants benefit equally and that no infant is subjected to the risk of early death from sickle cell disease because the screening test was not performed.

Screening programs targeting a specific racial or ethnic group will not identify all infants with sickle

cell disease, because it is impossible to define reliably an individual's racial or ethnic background by physical appearance, surname, or self-report.

Laboratory Issues

Blood Samples

- To obtain reliable results, blood samples for sickle cell screening must be collected prior to transfusion.
- Blood samples collected from the infant by heel stick onto filter paper are preferred for sickle cell screening because shipment to the laboratory is easy. This collection method is currently employed for other screening programs including those for phenylketonuria, hypothyroidism, and galactosemia.
- Liquid blood samples, obtained from the umbilical cord or directly from the infant, are acceptable alternatives but are more expensive and difficult to transport to the screening laboratory.

Testing Methods

- Hemoglobin electrophoresis, isoelectric focusing, and high performance liquid chromatography are all proven, reliable, and accurate methods for defining an infant's hemoglobin phenotype.
- Globin DNA analysis is an additional testing method, though this method requires considerable expertise and is costlier than the more established methods.
- The methods chosen for screening newborns should have high rates of sensitivity and specificity for identification of newborns with sickle cell disease and other clinically important hemoglobinopathies.

Note: Neither the sodium metabisulfite sickle cell preparation nor solubility tests employing a concentrated phosphate buffer and sodium dithionate should be used for newborn screening or confirmation of Hb S in early infancy.

Laboratory Qualifications

All testing should be done by laboratories that are licensed by their respective States or territories and that meet the requirements of the Clinical Laboratory Improvement Act of 1988 (CLIA 88).

Laboratory testing should be linked to other existing newborn screening programs within the jurisdiction to facilitate specimen collection, identification, handling, and result reporting.

Quality Assurance and Quality Control

The screening program must monitor all aspects of the screening process from sample collection to confirmation of diagnosis and tracking of infants to ensure that those with positive screening tests are retested and that infants with confirmed diagnoses are entered into comprehensive care.

Laboratories must participate in a proficiency testing program and, when feasible, should retest at least a sample of all newborns screened to determine the sensitivity and specificity of its screening methodology.

Reporting of Screening Results

Screening laboratories should maintain accurate records and are responsible for promptly communicating test results to the infant's health care provider of record, hospital of birth, the screening program's administrative component, and when permitted by law, to the infant's mother.

Reporting of the screening result should include the hemoglobin phenotype and mention the diagnostic possibilities associated with the phenotype. Reports to health care providers and mothers should list sources of additional information. The report must clearly indicate the likelihood that the infant may have sickle cell disease and stress the urgency for immediate followup.

Medical Management

Responsibilities of Health Care Providers

- Assignment of definitive diagnosis is the responsibility of the infant's physician. Physicians unfamiliar with diagnostic criteria should seek consultation from hematologists knowledgeable about sickle cell disease, thalassemia, and other hemoglobinopathies.
- When a newborn tests positively for sickle cell disease or other hemoglobinopathy, health care providers should immediately contact the parents to inform them of the need for the infant's immediate evaluation and retesting.
- Since newborn screening does not establish a definitive diagnosis, a second sample must be collected from the infant. In addition to defining the hemoglobin phenotype, the second specimen should be used to determine a complete blood count with red cell indices and assessment of red cell morphology.
- Characterization of the hemoglobin phenotype of the parents can be extremely helpful. The clinician must be aware that testing of the parents may disclose nonpaternity.
- DNA analysis of the infant's beta (ß) globin gene complex also may be used to establish a definitive diagnosis.
- Physicians and other health care providers must be aware that

any sign of illness in an infant with sickle cell disease is a potential medical emergency. Complications of sickle cell disease include, but are not limited to sepsis, acute chest syndrome, splenic sequestration crisis, aplastic crisis, stroke and hand-and-foot syndrome, and painful episodes.

- The physician or other health care provider is responsible for providing or arranging for appropriate education and genetic counseling for the parents.

Prophylactic penicillin

- Infants with documented or suspected sickle cell anemia or Hb S $ß^0$-thalassemia should be started on twice-daily oral prophylactic penicillin as soon as possible, but no later than 2 months of age.
- In those instances where the definitive diagnosis cannot be determined, an infant with the FS phenotype should be maintained on prophylactic penicillin until the definitive diagnosis is established.
- Prophylactic penicillin should be continued until at least 5 years of age.

Well-Baby Care

- Infants with sickle cell disease should receive standard well baby care. In addition to immunizations against polio, diphtheria, tetanus, measles, mumps, and rubella, children with sickle cell disease should be immunized against *Haemophilus influenzae* beginning at age 2 months and should receive polyvalent pneumococcal vaccine at age 2 years. Infants also should be immunized against hepatitis B virus.
- Diet should be monitored to ensure that the child with sickle cell disease is receiving all necessary nutrients and adequate calories. Multivitamins during the first 2 years of life may be appropriate.

Parental Instruction

- Health care providers must stress to parents the importance of twice-daily doses of prophylactic penicillin as an effective measure to reduce both morbidity and mortality from pneumococcal infections in infants with sickle cell anemia and HB S beta°-thalassemia.
- Parents of infants with sickle cell disease should be instructed in all aspects of routine child care and should be able to determine accurately the infant's temperature. They must be able to recognize complications of sickle cell disease, including the signs and symptoms of fever, pallor, and respiratory distress. Parents should be instructed on palpation of the infant's spleen and be taught to recognize splenic enlargement.
- The parents must understand the importance of prompt assessment of the infant by a physician knowledgeable about sickle cell disease when there is fever, pallor, unexplained irritability, diarrhea, vomiting, or other signs of illness.

Access to care

- Acutely ill infants with sickle cell disease should have access to tertiary care facilities that are staffed by pediatricians and pediatric surgeons knowledgeable about sickle cell disease.
- These facilities should include a sophisticated blood bank and clinical laboratories, as well as modern imaging equipment.

Education and Counseling

Principles

- A neonatal sickle cell screening program not only identifies infants with sickle cell disease, but also opens a "genetic window," which can result in the detection of other family members with sickle cell trait, sickle cell disease, or other hemoglobin diseases and heterozygotes for hemoglobin variants.
- Screening programs have an obligation to inform parents regarding their infant's result and to offer related education and counseling.
- Screening provides an invaluable opportunity to educate and counsel families.

Education

- Sickle cell education should include an explanation of the differences between the disease and the trait, prevalence of sickle cell trait and anemia in the U.S. population, the health status of persons with sickle cell trait, and the risks of having a child with sickle cell disease for persons with the trait.
- Information should be presented clearly using interactive techniques, appropriate graphics, and plain language. Easily understandable literature should be given to the parents to take home at the end of the education session.
- Parents should be offered the opportunity to be tested if they so desire.
- All adults testing positive for either Hb S, β^0-thalassemia trait, or a variant hemoglobin and those who have partners with either of these conditions also should be offered decision-making counseling.
- At a minimum, sickle cell educators should have a high school diploma and a certificate of competency in sickle cell education. The certifying process should be approved by the administrative component of the screening program and include successful completion of an examination that assesses knowledge of the material.
- The educator's skills should be evaluated periodically, and their sickle cell knowledge base should be updated annually.

Decision-Making Counseling

- Decision-making counseling should provide objective information about sickle cell disease and trait to individuals who are at risk of having a child with sickle cell disease. It should include specific information on the natural history of the type of sickle cell disease that may affect the individual's offspring and the resources that may be required to care for the child. This empowers the prospective parents to make informed decisions.
- Decision-making counseling must always be objective and should not offer specific recommendations. The counseling atmosphere must be private and conducive to a free exchange of information.
- Counseling should be done by professionals with backgrounds and training in guidance and counseling, such as physicians, clinical geneticists, genetic associates, medical social workers, and nurses.
- Quality assurance is an essential component of a genetic counseling program.

Conclusion

Although the prevalence of hemoglobin disorders differs among racial and ethnic groups, it is impossible to define reliably an individuals' race or ethnicity in a heterogeneous society like the United States. It is therefore recommended that screening programs provide equal access to health care by screening all infants for sickle cell disease and other hemoglobinopathies.

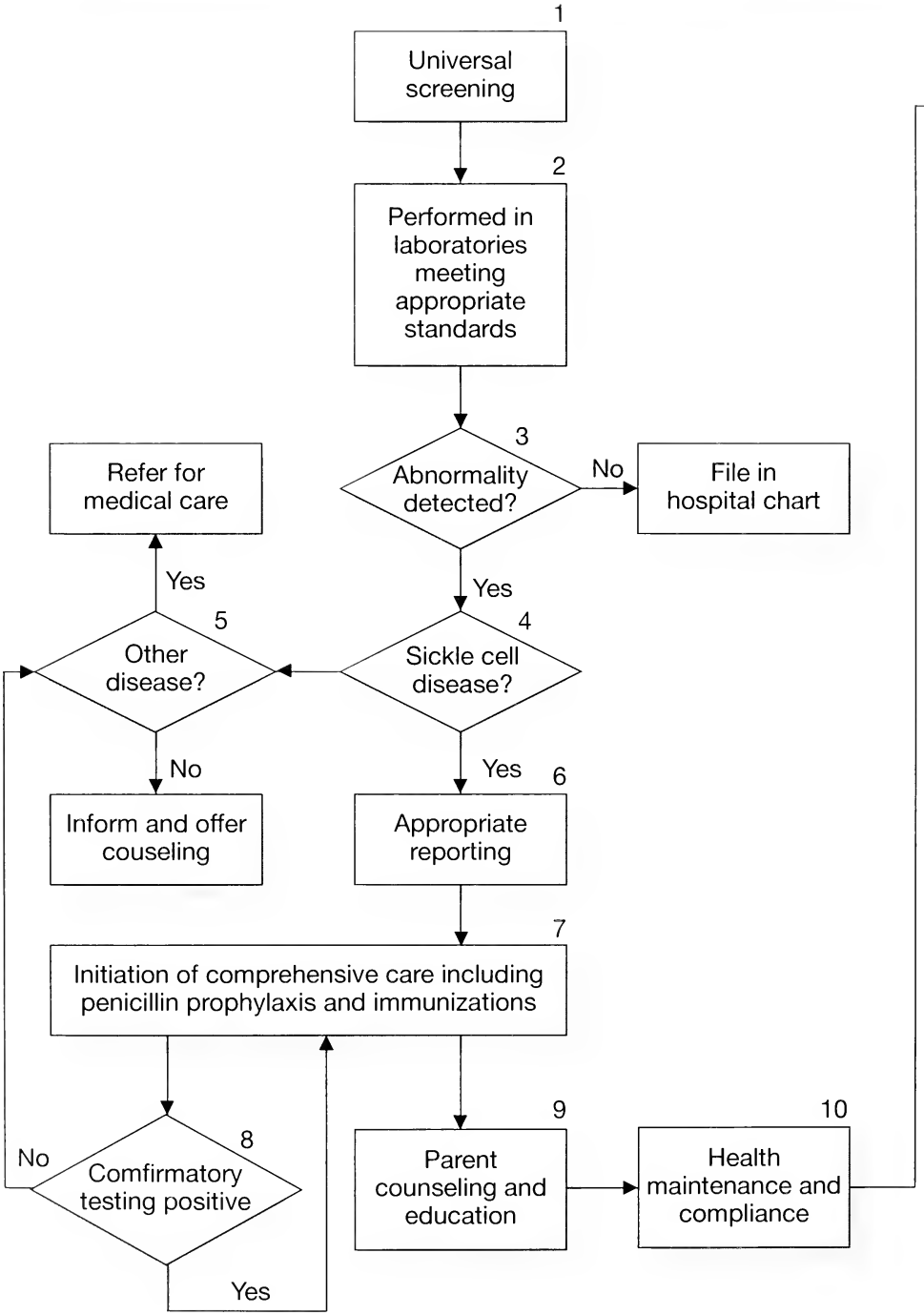
Screening programs should reduce costs through cooperative arrangements negotiated with other programs or with institutional or commercial laboratories to obtain the lowest cost per test for universal sickle cell screening.

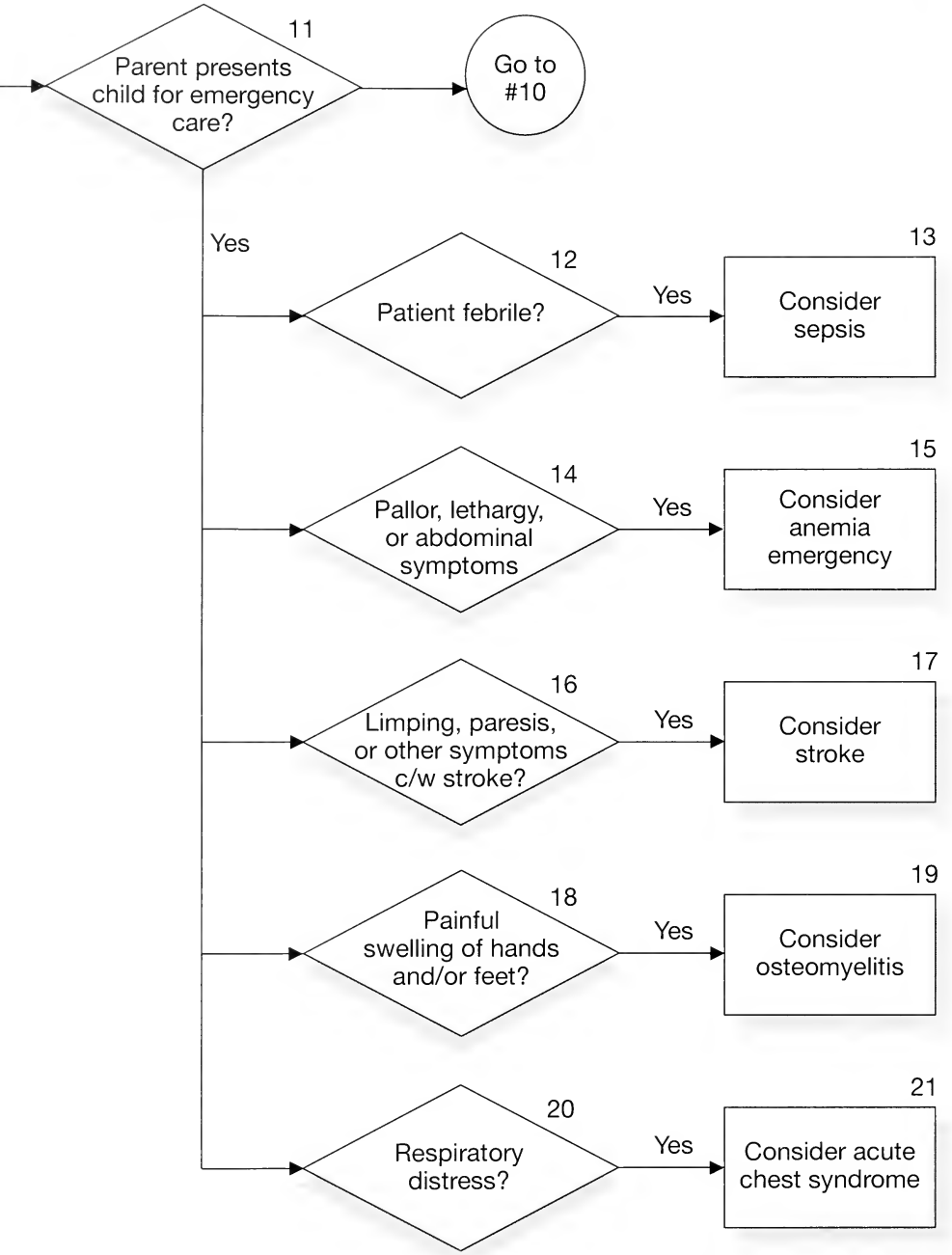
Algorithm

The algorithm on pages 8 and 9 presents a visual display of the organization, procedural flow, and decision points in identifying and careing for newborns and infants with sickle cell disease, sickle cell trait, and other hemoglobinopathies and educating and counseling their parents. Numbers in the algorithm refer to the annotations that follow.

Note: All chapter references are to the complete *Clinical Practice Guideline, Sickle Cell Disease: Screening, Diagnosis, Management, and Counseling in Newborns and Infants.*

Detection and Management of Sickle Cell Disease: An Algorithm




11
Parent presents child for emergency care?
Go to #10
Yes
12
Patient febrile?
Yes
13
Consider sepsis
14
Pallor, lethargy, or abdominal symptoms
Yes
15
Consider anemia emergency
16
Limping, paresis, or other symptoms c/w stroke?
Yes
17
Consider stroke
18
Painful swelling of hands and/or feet?
Yes
19
Consider osteomyelitis
20
Respiratory distress?
Yes
21
Consider acute chest syndrome

Universal screening

1. The panel concluded that universal newborn screening should be conducted to detect sickle cell disease. This conclusion is based both on considerations of practicality and cost-effectiveness. Screening for hemoglobinopathies should be conducted in parallel with other conditions routinely screened for in newborns.

Performed in laboratories meeting appropriate standards

2. The panel concluded that sickle cell screening should be performed only in laboratories that meet appropriate standards of performance and reporting. Quality assurance activities and appropriate reporting practices are discussed in Chapter 2.

The panel concluded that any of three methods are acceptable for sickle cell screening: (1) hemoglobin electrophoresis, (2) isoelectric focusing, and (3) high performance liquid chromatography. All are considered reliable and accurate. Metabisulfite sickle cell preparations and solubility testing, however, are not acceptable screening methods for newborns and should not be used to confirm the presence of hemoglobin S in newborns and infants.

Blood samples for testing may be submitted as anticoagulated blood from the umbilical cord or as dried blood spots collected onto filter paper. Each method has advantages and disadvantages. Filter paper samples are more easily integrated into existing newborn screening programs.

Abnormality detected?

3–4. The common types of sickle-cell abnormalities are discussed in Chapters 1 and 2.

Parents of sickle cell trait infants should be offered education and counseling. Couples at risk for having an infant with sickle cell disease should be offered decision-making counseling.

Other disease?

Parents of infants with other diseases or heterozygote conditions should be offered education and counseling. Couples at risk for having a child with disease should be offered decision-making counseling.

5. The presence of another abnormal hemoglobin may warrant referral for medical care. Parents of children with trait should receive counseling. These issues are discussed in Chapters 1, 2, and 4.

Appropriate reporting

6. Reporting of preliminary screening results is discussed in Chapters 2 and 3.

Initiation of comprehensive care including penicillin prophylaxis and immunization

7. Children with sickle cell disease identified on screening examination should be referred to a comprehensive care program without delay. Because confirmatory testing may not be complete for several weeks or months, it is important not to delay the basic elements of care, as described in nodes 9-12.

The panel concluded that prophylaxis against pneumococcal infection is warranted in all children with sickle cell anemia and sickle beta°-thalassemia. Administration of twice-daily oral penicillin has been demonstrated to reduce morbidity and mortality in these children. Children with sickle cell anemia also are at high risk for pneumococcal and *Haemophilus influenzae* infections. Immunization is extremely important (Chapter 3) and should be initiated by 2 months of age.

Confirmatory testing positive?

8. All positive screening tests for sickle cell disease require a second blood sample to confirm the initial hemoglobin phenotype. A definitive diagnosis should be established by the infant's physician.

Counseling and education of parents

9. Parents of infants with sickle cell disease must be counseled concerning the implications of their child's condition. Specifically, parents should be informed about the need for close vigilance with respect to the development of signs and symptoms that could indicate a serious medical problem. Any of the following warrant immediate medical consultation: (1) fever, (2) symptoms of respiratory tract infection, (3) increasing pallor, (4) increasing spleen size or abdominal distension, (5) weakness or numbness of an extremity, and (6) painful swelling of hands and feet. Information also should be provided concerning diet and adequate hydration. Parents should be trained in home management skills and should receive genetic counseling (Chapters 3 and 4).

Health maintenance and compliance

10. The schedule of health maintenance visits need not differ from that used for a well child. Strenuous efforts must be made by the health care provider to ensure compliance with penicillin prophylaxis (Chapter 3).

Parent presents child for emergency care?

11. Parents should be encouraged to seek immediate medical attention whenever the warning signs described in node 12 are noted.

Patient febrile?

12. Fever over 101°F (38.5°C) requires immediate medical evaluation. The parent also should be told that changes in behavior (unusual somnolence or irritability) or alimentation (refusing feeding, vomitting or diarrhea) are other possible early signs of significant illness.

Consider sepsis

13. It is critical that all health care providers who care for patients with sickle cell disease be knowledgeable about the significance of fever in these children. The importance of evaluating febrile sickle cell children promptly and administering broad spectrum antibiotics are emphasized. Management of febrile children with sickle cell disease is discussed in Chapter 3.

Pallor, lethargy, and abdominal symptoms?

14–15. Acute anemia emergencies are common in children with sickle cell disease, particularly acute splenic sequestration and aplastic crises. Diagnosis and management of these conditions are discussed in Chapter 3.

Limping, paresis, or other symptoms compatible with stroke?

16–17. Although relatively infrequent, both parents and providers must be alert for the possibility of a stroke. Any loss of consciousness or weakness of an extremity should be evaluated promptly.

Painful swelling of hands and feet?

18–19. The most frequent early complication of sickle cell disease is the hand-and-foot syndrome, or dactylitis (Chapter 3).

Bibliography

Charache S, Lubin B, Reid CD. Management and therapy of sickle cell disease. NIH Pub. No. 89-2117. Washington: U.S. Government Printing Office.

Consensus Conference. Newborn screening for sickle cell disease and other hemoglobinopathies. JAMA 1987 Sep;258(9):1205-9.

Newborn screening for sickle cell disease and other hemoglobinopathies. Pediatrics 1989;83(Suppl):813-914.

Leikin SL, Gallagher D, Kinney TR, et al. Mortality in children with sickle cell disease. Cooperative study of sickle cell disease. Pediatrics 1989;84:500-8.

Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia: a randomized trial. N Engl J Med 1986;314:1593-9.

Steinberg MH, editor. Newborn screening for hemoglobinopathies: program development and laboratory methods. Bethesda (MD): National Heart, Lung, and Blood Institute; 1990.

Whitten CF, Nishiura EN: Sickle cell anemia: public policy issues. In Hobbs N, Perrin JM, eds, Issues in the care of children with chronic illness. San Francisco: Jossey-Bass; 1985.

Sickle Cell Disease Guideline Panel. Sickle Cell Disease: Comprehensive Screening and Management in Newborns and Infants. Quick Reference Guide for Clinicians, No 6. AHCPR Pub. No. 93-0563. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, Department of Health and Human Services. April 1993.

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